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# Training-induced improvements in postural control are accompanied by alterations in cerebellar white matter in brain injured patients

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## ABSTRACT

We investigated whether balance control in young TBI patients can be promoted by an 8-week balance training program and whether this is associated with neuroplastic alterations in brain structure. The cerebellum and cerebellar peduncles were selected as regions of interest because of their importance in postural control as well as their vulnerability to brain injury. Young patients with moderate to severe TBI and typically developing (TD) subjects participated in balance training using PC-based portable balancers with storage of training data and real-time visual feedback. An additional control group of TD subjects did not attend balance training. Mean diffusivity and fractional anisotropy were determined with diffusion MRI scans and were acquired before, during (4 weeks) and at completion of training (8 weeks) together with balance assessments on the EquiTest® System (NeuroCom) which included the Sensory Organization Test, Rhythmic Weight Shift and Limits of Stability protocols. Following training, TBI patients showed significant improvements on all EquiTest protocols, as well as a significant increase in mean diffusivity in the inferior cerebellar peduncle. Moreover, in both training groups, diffusion metrics in the cerebellum and/or cerebellar peduncles at baseline were predictive of the amount of performance increase after training. Finally, amount of training-induced improvement on the Rhythmic Weight Shift test in TBI patients was positively correlated with amount of change in fractional anisotropy in the inferior cerebellar peduncle. This suggests that training-induced plastic changes in balance control are associated with alterations in the cerebellar white matter microstructure in TBI patients.

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## 1. Introduction

Traumatic brain injury (TBI) is a main cause of disability in children and adolescents worldwide (Atabaki, 2007). Besides neurobehavioral and cognitive problems, many patients with TBI are faced with motor deficits including postural instability, which can severely affect their level of independence and risk of falls (Chaplin et al., 1993; Kuhtz-Buschbeck et al., 2003; Rossi and Sullivan, 1996). Postural instability is often a long term consequence of TBI (Rossi and Sullivan, 1996). Using

instrumented measures of body sway, balance deficits have been observed months or even years after the traumatic incident in children (Caeyenberghs et al., 2010) and adults (Geurts et al., 1996; Kaufman et al., 2006; Basford et al., 2003).

Postural instability is associated with a dysfunctional structural brain network. Because postural control depends on complex sensorimotor integration, exchange of information among several brain regions is required. Our previous diffusion MRI work in young TBI patients (8–20 years) demonstrated that lower performance on a postural control task is associated with lower white matter (WM) anisotropy in specific sensorimotor pathways/regions, including the cerebellum and its peduncles (Caeyenberghs et al., 2010). Using a graph theoretical approach, a decreased connectivity degree in the cerebellum and parietal gyrus was found to be significantly correlated with poorer balance performance in TBI patients (aged 8–20 years; Caeyenberghs et al., 2012).

The cerebellum is of particular interest when considering balance impairments in TBI patients. Not only is it one of the most important

*Abbreviations:* ICP, inferior cerebellar peduncle; LOS, Limits of Stability; MCP, middle cerebellar peduncle; RWS, Rhythmic Weight Shift; SCP, superior cerebellar peduncle; SOT, Sensory Organization Test; TBI, traumatic brain injury; TBI-t, TBI group with training; TD, typically developing; TD-c, TD group without training; TD-t, TD group with training; UF, uncinate fasciculus.

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structures for the maintenance of postural stability (Morton and Bastian, 2004), it is often affected in TBI patients, even when the initial injury did not involve the cerebellum (Spanos et al., 2007; Soto-Ares et al., 2001). This is further supported by studies using animal models of indirect and direct TBI trauma (Igarashi et al., 2007; Park et al., 2006; Park et al., 2007). Moreover, functional (compensatory) and structural cerebellar changes have been reported in TBI patients as compared to controls (Caeyenberghs et al., 2010; Caeyenberghs et al., 2009).

A recent study showed that postural stability in a small sample ( $n = 5$ ) of young TBI patients (aged 7–13) was improved following a 6 week program of sit-to-stand and step-up exercises (Katz-Leurer et al., 2009). However, the neural underpinnings of exercise-induced rehabilitation in TBI patients remain largely unknown. Animal models of TBI suggest that neural plasticity can be initiated through exercise-induced up-regulation of neurotrophins in the brain (Griesbach et al., 2004; Kleim et al., 2003) which are related to neuronal growth and axonal regeneration (Barde, 1989; Lykissas et al., 2007). Moreover, a growing number of structural MRI studies have reported significant changes in brain structure in the adult human brain following motor training, even after a relatively short time. For example, Taubert and colleagues showed significant changes in gray matter (GM) volume and WM microstructure in several frontal and parietal regions, as well as in the right cerebellar WM, after two 45 minute sessions of dynamic balance training that correlated with skill improvement within a group of healthy young adults (aged  $25.9 \pm 2.8$  years; Taubert et al., 2010). Such MRI evidence of adult structural plasticity after balance training has also been shown in Parkinson patients (Sehm et al., 2014) and patients with cerebellar degeneration (Burciu et al., 2013). However, the latter two clinical studies were done in older age groups (average age of samples  $>53$  years) and were focused on GM volumetric changes. Here, we investigated whether training-induced improvements in balance are associated with neuroplastic adaptations in cerebellar WM in young TBI patients using diffusion MRI metrics.

We hypothesized that 8 weeks of balance training would result in significant balance improvements in young TBI patients, particularly when tested in compromising conditions with reduced sensory inputs and/or in more dynamic postural task conditions. Second, we predicted training-induced alterations in WM organization of the cerebellum and cerebellar peduncles, expressed as changes in fractional anisotropy (FA) and mean diffusivity (MD). Moreover, we expected these alterations to be correlated with improvements in balance performance. Thirdly, we inquired whether inter-individual differences in cerebellar WM structure at the start of training are predictive of postural balance improvements with training.

## 2. Materials and methods

### 2.1. Subjects

A total of 48 young participants were recruited, including a group of 29 typically developing (TD) subjects and a group of 19 TBI patients. All TBI patients participated in the training program (TBI-t group,  $M_{\text{age}} = 14$  years,  $SD = 3$  years, 9 males 10 females). From the 29 TD subjects, 19 were included in the training protocol (TD-t group,  $M_{\text{age}} = 15$  years,  $SD = 2$  years, 8 males 11 females). The remaining 10 TD subjects were recruited for a follow-up without training (TD-c group  $M_{\text{age}} = 15$  years,  $SD = 2$  years, 4 males 6 females) to test for stability/reproducibility of the MRI acquisitions, possible maturation effects, and familiarization with the test protocol. Because such a control group is lacking in many studies on training-related changes in brain structure (Thomas and Baker, 2013), this is a distinctive feature of the present study. Moreover, this TD-c group also distinguishes the present study from previous balance training paradigms looking into brain-behavior changes. An extra group of TBI subjects without training was also considered. However, difficulties associated with recruitment of a reasonable sample size of TBI patients precluded us to do so.

Furthermore, it was assumed that possible familiarization/maturation effects were limited and largely similar across subjects (TD and TBI).

All TBI subjects (TBI-t group) experienced moderate to severe TBI and did no longer participate in acute inpatient rehabilitation. They were tested at least 4 months post-injury when neurological recovery was stabilized, corresponding to the sub-acute ( $>2$  weeks) and chronic ( $>1$  year) stages of injury. The mean interval between the injury and the first test session was 3 years and 8 months ( $SD = 3$  years 3 months). The mean age at injury was 10 years and 1 month ( $SD = 3$  years 3 months). All TBI subjects were recruited from rehabilitation centers in Belgium. For the classification of the injury, we used commonly applied TBI severity indicators in accordance with the Mayo classification system (Malec et al., 2007). All TBI patients were classified as ‘moderate-to-severe’, based on the presence of one or more of the following criteria: loss of consciousness of 30 min or more; worst Glasgow Coma Scale score in the first 24 hours lower than 13, or evidence of contusions, microbleeds or hematoma on CT or MRI images made immediately after the injury. Moreover, a T1-weighted anatomical scan was administered before the onset of the training and was inspected and classified by an expert neuroradiologist (Table 1). All subjects were able to maintain postural stability during independent stance. Exclusion criteria for both groups were pre-existing developmental disorders, central neurological disorders, intellectual disabilities and musculoskeletal disease.

Control children were recruited from primary and secondary schools in Belgium. The study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the local ethics committee for biomedical research. Consent was obtained from all subjects and their parents.

### 2.2. Training

Subjects attended a home-based balance training program for 8 weeks. A computer-assisted training method was used, which was particularly well suited for our young subject group. Participants in both training groups were instructed to train for five sessions per week with approximately 30 min per session, using two portable platforms for balance control in home settings: the Pro-balance and the Balanco (Fysiomed NV, Edegem, Belgium, Fig. 1).

The Pro-balance system (Fig. 1A and B) is a portable balancer which can be connected to a laptop, providing real-time visual feedback (Ang et al., 2008). Participants could choose different games, each lasting 2 min, in which they had to move their center of gravity in order to tilt the platform forward, backward or sideways. The Balanco is a wobble board provided with three interchangeable game surfaces (Fig. 1C). Each training session consisted of 14 min of exercise on the Pro-balance (seven games of 2 min) and another 14 min of exercise on the Balanco. The estimated total training time was 1120 min (=18.7 hours). The progression and compliance of the participants to the training protocol were carefully monitored through regular contact of the research team with the participant’s parents (e-mails and phone calls). Moreover, the Pro-balance computer system registered training duration and the subjects also kept a logbook of their training.

From the 19 TD-t subjects, two subjects were not able to finish the program (i.e. not completing the mid- and post-tests) due to the time-consuming nature of the training. In these cases, the measurements from the pre-test were still included in the statistical model (as described below). In one subject we were not able to acquire scans during the pre-test due to technical problems. In summary, we acquired complete datasets from 16 TD-t subjects. The 10 subjects of the TD-c group underwent the exact same measurements at the same time intervals but did not attend any balance training activities. From the 19 TBI-t subjects, four subjects were not able to finish the training due to lack of time ( $n = 3$ ) or because of the high physical load ( $n = 1$ ). The measurements from the pre-test of these subjects were included in the statistical model. To summarize, we acquired a complete three-test-session dataset from 15 TBI patients.

**Table 1**

Demographic and injury characteristics for the TBI-T group.

TBI patient #: Age (y)/gender/cause of injury/age at injury (y)/time since injury (y)	GCS/coma duration	Test-sessions included in final analysis	Lesion location/pathology based on MRI scan at pre-test	Lesion location/pathology based on acute MRI scan within 24 hours after injury
TBI 01; 8.6/M/traffic accident/7.9/0.7	Coma = 5 days	Pre–mid–post	Hemosiderin deposits: R semiovale center and CC	Subdural hematoma R FL/PL/TL; cortical contusion R FL/PL; DAI in R FL
TBI 02; 18.1/F/traffic accident/15.6/2.5	Coma = 5 days	Pre–mid–post	Small injuries surrounding drain trajectory in RH (superior frontal gyrus, head of caudate nucleus, crus anterior of internal capsule, thalamus and pons)	Subdural hematoma/hemorrhagic contusion TL/FL; injuries R FL, thalamus, R cerebral peduncle, L mesencephalon; cortical and subcortical hemorrhagic areas in PL/TL
TBI 03; 9.3/F/traffic accident/7.9/1.4	Coma = 2 weeks	Pre–mid–post	Contusion: R anterior temporal pole and R orbitofrontal cortex; injuries and atrophy in CC (body and splenium); atrophy of R pons; hemosiderin deposits in L cerebellar hemisphere, R nucleus lentiformis, L/R FL, L/R PL and R PL	DAI in L TL/FL, R TL/FL/PL
TBI 04; 16.5/F/traffic accident/7.2/9.3	NA	Pre–mid–post	Injuries in R medial frontal gyrus	Epidural hematoma R FL/TL; shift midline
TBI 05; 14.2/F/traffic accident/7.7/6.5	NA	Pre–mid–post	Atrophy of the cerebellum; injuries at the level of L FL, premotor cortex, L/R medial frontal gyrus, cingulum, orbitofrontal cortex (L > R); contusion anterior temporal pole (R > L); hemosiderin deposits in CC, L thalamus, striatum (R > L)	NA
TBI 06; 13.4/M/traffic accident/12.5/0.8	LOC (unknown duration)	Pre–mid–post	Hemosiderin deposits: several spread out over L/R PL, R cerebellum, L superior frontal gyrus. Hemosiderosis as a remnant of subdural hemorrhage	Hemorrhagic contusion L TL; brain edema
TBI 07; 17.1/F/traffic accident/12.7/4.4	GCS = 3, Coma = 6 weeks	Pre–mid–post	Contusion/atrophy: R superior frontal gyrus, R temporal gyrus; injuries at the level of the R supramarginal gyrus, R angular gyrus, R precentral gyrus (M1), central sulcus, R postcentral gyrus, R medial frontal gyrus, R insula, R head and body of caudate nucleus, R globus pallidus, R putamen, anterior part of R thalamus; hemosiderin deposits in LH (superior/inferior frontal gyrus, paraventricular WM) and several in RH	Atrophy across whole brain: R FL/TL (with hemosiderin deposits), nucleus caudatus and R nucleus lentiformis, R mesencephalon, R PL (with surrounding gliosis); cerebellum (specifically L posterior hemisphere); hemosiderin deposits (DAI): L FL, thalamus, TL, R OL. Shift of midplane; enlarged R lateral ventricle (with surrounding gliosis)
TBI 08; 19.0/F/fall/12.5/6.5	LOS (unknown duration)	Pre–mid–post	Hemosiderin deposits R cerebellar vermis	Subdural hematoma L FL/TL/PL
TBI 09; 15.6/m/traffic accident/12.5/3.2	Coma = 10 days	Pre–mid–post	Atrophy cerebellum; contusion R FL WM	DAI R TL, internal capsule, supra-orbital R FL, L FL WM (anterior corona radiata), L middle cerebellar peduncle
TBI 10; 13.9/m/traffic accident/13.5/0.3	GCS = 3	Pre–mid–post	Hemosiderin deposits: L FL, periventricular WM, body and genu CC, L thalamus, R external capsule, anterior TL (L > R), L/R cerebellum; limited atrophy cerebellum	DAI FL, TL, L OL (hemorrhagic injury), R TL, cerebellum, CC, external capsule, R globus pallidus, L thalamus, R cerebral peduncle, R mesencephalon
TBI 11; 8.5/F/traffic accident/7.7/0.8	NA	Pre–mid–post	Enlarged fourth ventricle, atrophy of cerebellar vermis, contusion R cerebellar vermis, hypotrophy of middle cerebellar peduncle and L pons; contusion L TL; hemosiderin deposits R FL, L TL, vermis	NA
TBI 12; 10.9/M/sports injury (equestrian)/7.9/3.1	GCS = 4, LOC (unknown duration)	Pre–mid–post	Injuries in RH: orbitofrontal cortex, inferior frontal gyrus and anterior part of medial/superior frontal gyrus; hemosiderin deposits in L superior frontal gyrus and L cerebellar hemisphere	Hemorrhagic contusion FL/TL, subdural hematoma L FL
TBI 13; 11.4/M/sports injury (equestrian)/9.8/1.5	Coma (unknown duration)	Pre–mid–post	Hemosiderin deposit: splenium CC	Contusion L FL/TL; enlarged, asymmetric ventricle (temporal horn)
TBI 14; 13.3/M/traffic accident/12.1/1.2	LOC = 15 min	Pre–mid–post	Hemosiderin deposits L FL, genu CC	DAI in genu and splenium CC, L FL
TBI 15; 13.3/M/traffic accident/12.8/0.5	LOC = 20 min	Pre–mid–post	Shearing injuries in body and genu CC; mild WM loss (enlarged ventricles); hemosiderin deposits L/R paramedian FL, R thalamus, several in L temporal pole, L cerebellum, L OL	Contusion L FL/TL; DAI (incl some hemorrhagic injuries) in FL, L PL/OL, genu CC, L cerebellum; subdural hygroma FL (R > L)
TBI 16; 14.1/F/sports injury (ski)/6.0/8.0	LOC (unknown duration)	Pre	No or small tissue damage	Small injury R FL
TBI 17; 16.0/F/NA/NA/NA	NA	Pre	Mild atrophy in cerebellum and cerebrum, more pronounced atrophy in frontal cortices, enlarged ventricles; contusion L/R anterior temporal pole and L/R orbitofrontal cortex. Hemosiderin deposits in cerebellum, R FL	NA
TBI 18; 17.8/M/NA/12.2/5.7	NA	Pre	Hemosiderin deposits: thalamus, L TL, L/R parietal	Hemorrhagic contusion L FL, atrophy L FL
TBI 19; 13.8/F/object against head/3.0/10.8	NA	Pre	Contusion: L anterior middle frontal gyrus and L anterior superior frontal gyrus	

Anatomy codes: WM = white matter; RH = right hemisphere; LH = left hemisphere; FL = frontal lobe; TL = temporal lobe; PL = parietal lobe; OL = occipital lobe; CC = corpus callosum; R = right; L = left. Other codes: y = years; GCS = Glasgow Coma Scale score; M = male; F = female; NA = Information not available.



**Fig. 1.** A) Pro-balance. The tilt of the platform was represented by a cursor on the screen. The cursor was moved using center of gravity displacements. Games were either aimed at making smooth and precise movements or quick weight shifts. B) Sliders on the bottom of the system enabled us to change the stability of the platform and adjust it to the participants' performance level. C) Balanco balance board with 3 interchangeable game surfaces through which a ball can be directed by making weight shifts.

### 2.3. Assessment

Participants underwent a baseline measurement prior to the training (pre-test), a measurement after 4 weeks of training (mid-test, mean  $28 \pm 1$  days after pre-test) and a final measurement after 8 weeks of training (post-test, mean  $57 \pm 2$  days after pre-test). During each test session, the effect of training on measures of balance control (posturography) and brain microstructure (diffusion MRI parameters) were assessed.

#### 2.3.1. Posturography

The EquiTest System (NeuroCom International, Clackamas, Oregon) provides objective posturographic assessment of balance control under static and dynamic test conditions. The system contains a visual surround and a force plate that measures the vertical forces under the subject's feet. Balance control was tested using three test protocols on the EquiTest, including the Sensory Organization Test (SOT), the Limits of Stability test (LOS) and the Rhythmic Weight Shift test (RWS). All tests were performed bare-foot and with a safety harness. The total administration time of the three tests was approximately 20 min.

The SOT is a measure of static postural control in which the subject is instructed to stand on the platform (forceplate) as still as possible while sensory resources (i.e. somatosensory inputs, visual inputs or both) are systemically disrupted. The LOS and RWS are more dynamic tests of balance control requiring goal directed postural adjustments. During the test, the subjects intentionally displaced their center of gravity in different directions without stepping, falling, or lifting the heel or toes. In contrast to the static SOT protocol, the RWS and LOS tasks both require target-aimed postural adjustments and did therefore have some resemblance with the balance exercises on the balance boards that were practiced during training.

For each of the tests a balance score was calculated based on the trajectory of the center of pressure during the task (see Supplementary material for an in-depth discussion of these test protocols).

#### 2.3.2. MRI data acquisition

MR examination was performed on a Siemens 3 T Magnetom Trio MRI scanner (Siemens, Erlangen, Germany) with a 12 channel matrix head coil. Before the first test session, the scanning equipment was introduced by means of a dummy scanner to ensure the participants' comfort with the scanning environment.

A DTI SE-EPI (diffusion weighted single shot spin-echo echoplanar imaging) sequence ( $[TR] = 8000$  ms,  $[TE] = 91$  ms, voxel size =  $2.2 \times 2.2 \times 2.2$  mm<sup>3</sup>, slice thickness = 2.2 mm,  $[FOV] = 212 \times 212$  mm<sup>2</sup>, 60 contiguous sagittal slices covering the entire brain and brainstem) was acquired. A diffusion gradient was applied along 64 noncollinear directions with a b-value of 1000 s/mm<sup>2</sup>. Additionally, one set of images with no diffusion weighting ( $b = 0$  s/mm<sup>2</sup>) was acquired.

Moreover, a high resolution T1-weighted image was acquired for anatomical detail using a 3D magnetization prepared rapid acquisition

gradient echo (MPRAGE; repetition time  $[TR] = 2300$  ms, echo time  $[TE] = 2.98$  ms, voxel size =  $1 \times 1 \times 1.1$  mm<sup>3</sup>, slice thickness = 1.1 mm, field of view  $[FOV] = 256 \times 240$  mm<sup>2</sup>, 160 contiguous sagittal slices). These structural MRI scans were examined by an expert neuro-radiologist as described previously (see Subsection 2.1). The scan time for the T1 and diffusion MRI scans was approximately 25 min.

#### 2.3.3. Diffusion MRI processing

The diffusion MRI data were analyzed and processed in ExploreDTI (Leemans et al., 2009) using the following multi-step procedure (for a more extensive description, see Caeyenberghs et al., 2011): (a) raw data quality was visually checked (inspection of a loop through the separate raw diffusion-weighted images, inspection of orthogonal views, inspection of residuals and outliers), (b) geometrical distortions induced by subject motion and eddy currents were corrected (Leemans, and Jones, 2009) (c) the diffusion tensors and subsequently the diffusion parameters were calculated using a non-linear regression procedure (Mori et al., 2008), and (d) DTI data were transformed to MNI space. First, a population-based MNI template was constructed (Mori et al., 2008; Van Hecke et al., 2008). With this template, an affine, and subsequently a high dimensional non-affine DTI-based coregistration technique could be applied to obtain the final DTI data sets in MNI space (Leemans et al., 2005; Van Hecke et al., 2007). In the nonaffine coregistration approach, the images are modeled as a viscous fluid, imposing a constraint on the local deformation field. During normalization, the Jacobian is constrained to reduce the chance of forcing the underlying brain structures in an anatomically nonplausible way. This viscous fluid model was optimized for aligning multiple diffusion tensor components and has been applied successfully in a wide range of applications, where adjusting for morphological intersubject (and intergroup) differences, such as, for instance, ventricle size, is considered to be of paramount importance (Van Hecke et al., 2010; Sage et al., 2009; Verhoeven et al., 2010).

Fractional anisotropy (FA) and mean diffusivity (MD) were selected for further analysis as proxy markers of white matter microstructural organization. FA is the most commonly studied diffusion parameter which best captures the directional coherence in WM tissue. MD is more tolerant to changes in signal-to-noise ratio and could potentially provide insights into the different aspects of microstructural changes in white matter (Marenco et al., 2006; Pierpaoli, and Basser, 1996; Farrell et al., 2007). Additionally, for the tracts in which we found a significant training effect, axial diffusivity and radial diffusivity (AD and RD) were analyzed to gain more insights into possible underlying microstructural mechanisms of change.

#### 2.3.4. Region of interest (ROI) definition: cerebellum and cerebellar peduncles

As stated in the Introduction, we focused on the cerebellum and its major connecting WM pathways (cerebellar peduncles) as regions/ tracts of interest in view of their crucial role in sensory processing and



balance control and their vulnerability to traumatic injury. Using this anatomical hypothesis, an observer-independent atlas-based analysis was used to identify the following regions: Global cerebellum (digitized version of the Talairach atlas; Lancaster et al., 2000; Lancaster et al., 2007); and superior (left, right), middle and inferior (left, right) cerebellar peduncles (SCP, MCP and ICP; JHU white-matter tractography atlas; Mori et al., 2005). An additional exploratory analysis was performed on a set of additional (non-cerebellar) sensorimotor tracts (corticospinal tract, medial lemniscus and internal capsule) which can be viewed in the Supplementary material. Using these pre-parcellated WM regions, defined on the Mori template, we used registration tools to automatically transform these atlas labels to each individual subject which then allowed the calculation of our diffusion MRI measures of interest at the corresponding locations (Mori et al., 2008). Being objective and reproducible (important in longitudinal data-analyses), this procedure overcomes many of the limitations that accompany the manual ROI based approach. Fig. 2 shows a reconstruction of the cerebellar peduncles based on the JHU tractography atlas. The left and right SCP and ICP were averaged to one combined ROI for further analysis. The MCPs did not require averaging because this represents one single continuous structure in the JHU tractography atlas (connected through the pons). To obtain specificity for our anatomically driven hypothesis, we also included a control tract, i.e. the uncinate fasciculus (UF), which is mainly involved in cognitive processing (Aralasmak et al., 2006). It has been used previously as a control tract in a motor training study involving young brain injured patients (aged 7–17 years; Rocca et al., 2013). The left and right UFs were averaged for further analysis. To assure that averaging the left and right counterparts of the ICP, SCP and UF was warranted, additional analyses were performed showing that the difference between the left and right counterparts was not statistically significant and that side (left, right) did not interact with training (see Supplementary material).

#### 2.4. Statistics

Analysis of gender was assessed by a Chi-square test. We compared the mean age and the average total amount of completed training hours between the groups of interest using two-sample t-tests.

Pre-test data of balance control metrics (i.e. SOT, LOS and RWS balance scores) as well as brain metrics (FA and MD) of 5 ROIs were used for group comparisons because the measurements from the pre-test were not influenced by training effects. A priori contrasts of interest were used to reduce the number of contrasts: TBI-t vs TD-t and TD-t vs TD-c. These pre-test group comparisons were computed using the differences in least square means in the mixed model procedure (see below).

The balance control and brain metrics were further assessed by means of a mixed model procedure in SAS® software (version 9.3, SAS Institute Inc., Cary, NC). The factor group (three levels: TD-t, TD-c, TBI-t) was included as between-subjects variable and the factor time (three levels:

pre-, mid- and post-tests) as within-subjects variable. The level of significance was set to  $\alpha = 0.05$ . We specified an 'unstructured' covariance allowing the model to permit a different variance for each level of the included variables, thereby avoiding the assumption of sphericity. Also, while 'classical' repeated measure approaches discard all results from any subject with missing measurements, mixed models allow the available data on such subjects to be included. Subsequent pairwise comparisons of interest were made within each of the three groups between the time points (pre-, mid- and post-) and were Bonferroni corrected for the three comparisons within each group (pre- vs mid-, pre- vs post-, mid- vs post-). The p-values of the pairwise comparisons mentioned in the results are therefore Bonferroni adjusted values. Differences in least square means in the mixed model procedure were used to compute these comparisons using an lsmeans statement. This way, the dependency between time points (within subjects factor) was taken into account.

Our final aim was to investigate the relationship between brain structure and balance control before training (cross-sectional correlations) and throughout the training (longitudinal correlations), consisting of the following steps. First, cross-sectional correlations were computed using the balance control metrics and brain structure metrics (FA and MD) from the pre-test. Second, for the longitudinal correlations, difference scores for both balance performance and diffusion parameters were calculated as a measure of change by subtracting the pre-test scores from the post-test scores. Then, two sets of correlation analyses were conducted. On the one hand, difference scores in diffusion parameters (FA and MD) were correlated with difference scores in balance outcome (SOT, LOS and RWS scores) to investigate the relationship between change in brain structure and change in balance performance. On the other hand, we investigated whether the changes in performance as a result of training (balance difference scores) can be predicted by between-subject differences in cerebellar structure, as determined at pre-test. The latter cross-sectional metric of cerebellar structure provides a very different perspective on plasticity predicted by brain structure because it is not driven by the subtle within-subject changes in the cerebellum but by the larger and more robust between-subject differences in cerebellar structure. These correlations were computed for each of the 5 ROIs. The significance threshold was Bonferroni corrected for the number of ROIs, resulting in an effective alpha level of  $p < 0.01$ .

### 3. Results

#### 3.1. Group differences in demographics and balance training

The Chi-square test showed that there were no significant differences in gender composition between the three groups  $\chi^2 (2, n = 48) = 0.179, p = 0.80$ . No significant age differences were found between the TD-t and TD-c groups ( $t(27) = 0.12, p = 0.91$ ) and between the TD-t and TBI-t groups ( $t(36) = 1.37, p = 0.18$ ). Therefore, further analyses did not take into account the possible effects of gender and age. The mean total training time was 927 min (SD = 187 min) for the TBI-t group and 1029 min (SD = 120 min) for the TD-t group. The amount of training time did not statistically differ between the two groups, although a trend towards significance was observed ( $t(29) = 1.84, p = 0.08$ ). Mixed model analysis between the 11 patients identified with cerebellar damage (based on inspection of anatomical scans, see Table 1) and the other 8 patients, showed no interaction effects between group (presence of cerebellar damage) and time (training) in any of the ROIs or balance tests (all  $ps > 0.05$ ). We therefore combined all patients in a single group in further analyses to maintain a reasonable sample size. Pairwise comparisons of the pre-session data did however show that at baseline, patients with observed cerebellar damage had a lower FA in the cerebellum ( $t(24) = 2.38, p = 0.026$ ), MCP ( $t(26) = 2.52, p = 0.018$ ), as well as a higher MD in the MCP ( $t(26) = 2.19, p = 0.038$ ).

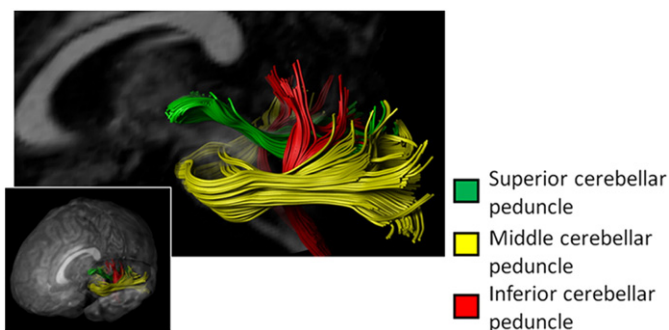


Fig. 2. A reconstruction of the cerebellar peduncles, displayed on a representative 3D fractional anisotropy image.

### 3.2. Group differences and training effects on postural control

Fig. 3 displays the means and standard errors at each test session (pre-, mid- and post-) in each of the three postural control tests (SOT, RWS and LOS) for each group. Comparisons between the pre-test scores exhibited a significant difference on the SOT ( $t(76) = 2.94, p < 0.01$ ) and the RWS ( $t(77) = 2.12, p < 0.05$ ) between the TBI-t group and the TD-t group with the former scoring significantly lower, reflecting a higher amount of body sway during the tasks. Important to note, no significant group effects on the postural control tests were found between TD-t and TD-c.

Mixed model analysis revealed a significant main effect of time for the SOT ( $F(2,75) = 6.34, p < 0.01$ ) and the RWS ( $F(2,77) = 5.95, p < 0.01$ ). As shown in Fig. 3, the direction of performance change was similar in both training groups. Pairwise comparisons (Bonferroni corrected) on the SOT revealed a significant increase from pre- to post-test for the TBI-t group ( $t(76) = 3.50, p < 0.001$ ) and a trend towards a significant increase from pre- to post-test for the TD-t group ( $t(76) = 2.37, p = 0.06$ ) (Fig. 3A). In the RWS-test, a significant increase was evident in the TBI-t group from pre- to post-test ( $t(77) = 2.43, p = 0.05$ ) as well as in the TD-t group from pre- to mid-test ( $t(77) = 3.99, p < 0.001$ ) and from pre- to post-test ( $t(77) = 4.11, p < 0.001$ ) (Fig. 3B).

Finally, in the LOS-test, both a main effect of time ( $F(2,76) = 9.63, p < 0.001$ ) as well as an interaction effect of time and group were found ( $F(4,76) = 3.46, p < 0.05$ ). Specifically, a significant increase in performance on the LOS-test was observed in the TD-t group between the pre-test and post-test ( $t(76) = 3.72, p < 0.01$ ). In the TBI-t group a significant increase was found from pre- to mid-test ( $t(76) = 4.35, p < 0.001$ ) and from the pre- to post-test ( $t(76) = 3.68, p < 0.001$ ) (Fig. 3C). No significant changes were observed in the TD-c group for any of the three postural control tasks.

### 3.3. Effect of group and training on white matter microstructure of the cerebellum

Here, we looked at between group comparisons between diffusion MRI metrics (FA and MD) obtained at pre-test as well as changes in diffusion metrics across the three test sessions. With respect to the first, comparisons between the TD-t and TBI-t groups at pre-test revealed a lower FA in the TBI-t group in the ICP ( $t(77) = 2.56, p < 0.05$ ) and SCP ( $t(77) = 2.76, p < 0.01$ ) as well as in the whole cerebellum ( $t(75) = 2.66, p < 0.01$ ) (see Fig. 4A).

MD values were significantly higher in the TBI-t than TD-t group in the ICP ( $t(77) = 2.22, p < 0.05$ ), MCP ( $t(77) = 2.62, p < 0.05$ ), SCP ( $t(77) = 2.56, p < 0.05$ ) and cerebellum ( $t(74) = 3.09, p < 0.01$ ) (Fig. 4B). No significant group differences were found between the TD-t group and TD-c group in FA or MD for any of the identified ROIs (Fig. 4).

With respect to changes in diffusion metrics across the three test sessions, the mixed model analysis revealed a significant effect of time in MD of the ICP ( $F(2,77) = 3.75, p < 0.05$ ) (see Fig. 5). The Group  $\times$  Time interaction did not reach significance ( $F(4,77) = 0.87, p = 0.48$ ). Subsequent a priori pairwise comparisons across test time points within each group revealed a significant increase in MD values between the pre- and post-tests in the TBI-t group ( $t(77) = 3.42, p < 0.005$ ), whereas this effect did not reach significance in the other groups (TD-t group:  $t(77) = 0.97, p = 0.33$ ; TD-c group:  $t(77) = 1.47, p = 0.15$ ) (see Fig. 5). The same mixed model analysis on FA did not reveal any significant main (or interaction) effects.

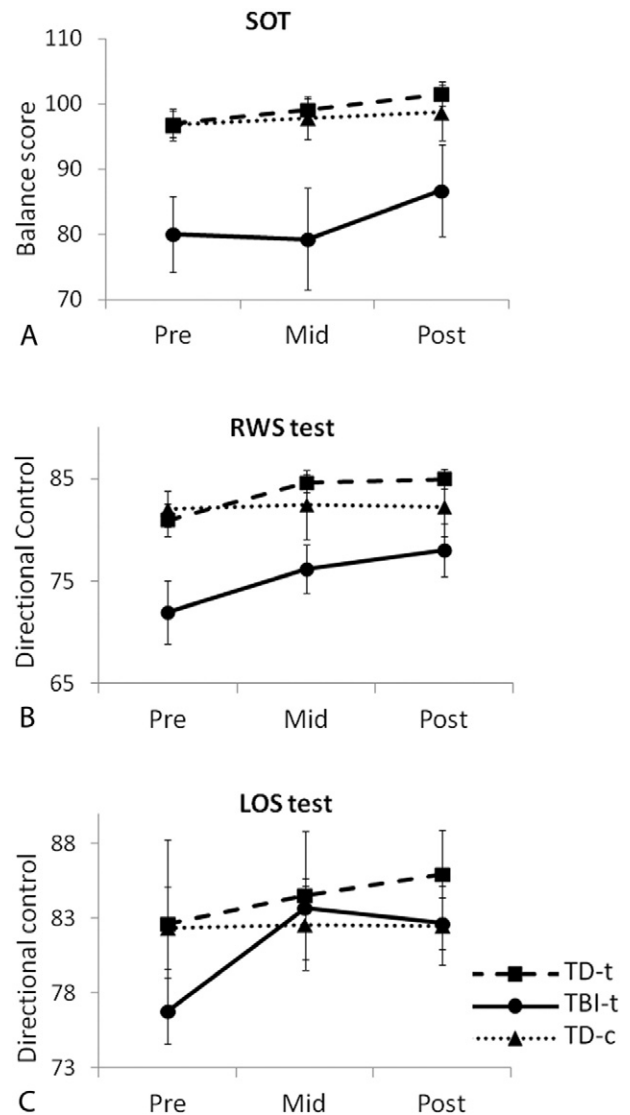
Analysis of AD and RD was conducted exclusively for the ICP for more detailed investigation of underlying mechanisms of the change in MD. At pre-test, RD was significantly higher in the TBI-t group as compared to the TD-t group ( $t(75) = 3.18, p < 0.01$ ). Furthermore, a significant main effect of time was revealed in AD of the TBI-t group ( $F(2,77) = 3.83, p < 0.05$ ) with a significant increase from pre- to post-test ( $t(77) = 4.59, p < 0.001$ ).

### 3.4. Baseline correlations between postural control and cerebellar structures

To establish the relationship between WM microstructure and postural control performance at baseline, correlations were determined between FA and MD at pre-test and balance performance at pre-test. Using a conservative Bonferroni corrected threshold, significant correlations were obtained in the TBI group between performance of the RWS task and FA in the cerebellum ( $r = 0.67, p < 0.01$ ) and SCP ( $r = 0.65, p < 0.01$ ) as well between performance of the RWS task and MD in the MCP ( $r = -0.65, p < 0.01$ ) and SCP ( $r = -0.70, p < 0.01$ ). Hence, higher balance levels on the RWS task were associated with higher FA and/or lower MD in several of the cerebellar WM structures. Additional correlations (including those at the explorative threshold of  $p < 0.05$ ) are reported in Table 2.

### 3.5. Relationships between training-induced changes in postural control and cerebellar structures

We determined whether the changes in balance performance as a result of training (post-test minus pre-test scores) were associated



**Fig. 3.** Results of the 3 balance tests over the time course of the training (error bars indicate SEM). Significant improvements: SOT) TD-t (pre-post); RWS) TBI-T group (pre-post) and TD-T group (pre-mid, pre-post); and LOS) TD-T group (pre-post), TBI-T group (pre-mid and pre-post).

with the structural characteristics of the cerebellar structures at pre-test.

Using an exploratory threshold, a significant negative correlation in the TBI-t group between FA of the ICP and change in LOS directional control was found ( $p < 0.05$ ,  $r = -0.54$ ) (Fig. 6A). In the TD-t group, baseline FA of the cerebellum was associated with change in RWS directional control on the one hand ( $p < 0.05$ ,  $r = -0.59$ ), and with change in SOT balance score on the other hand ( $p < 0.025$ ,  $r = -0.56$ ) (Fig. 6B and C). Hence, lower FA values coincided with increased improvements on the postural control task. A significant positive correlation was also found between MD in the MCP and change in RWS directional control ( $p < 0.05$ ,  $r = 0.50$ ), indicating that a higher MD is associated with a higher increase in performance on the RWS task (Fig. 6D).

Finally, correlation analysis was used to examine the relationship between changes in postural control and changes in diffusion parameters in all 5 ROIs. Using an exploratory uncorrected threshold of  $p < 0.05$ , the change in RWS directional control (post-test score minus pre-test score) was significantly related to FA change in the ICP in the TBI-t group ( $p < 0.026$ ,  $r = 0.57$ ) (see Fig. 6E). The larger the increase in FA was over time, the higher the training-related increase in balance performance. A similar positive correlation was also observed in the TD-t group between change in cerebellar FA and change (improvement) in SOT balance score with training ( $p < 0.05$ ,  $r = 0.56$ ) (see Fig. 6F). Although a change in MD was observed in the TBI-t group (see Subsection 3.3), this did not correlate with the change in the balance scores. No significant correlations were observed for the FA or MD in the UF.

### 3.6. Relationships between time since injury and training effects

We correlated the changes over the course of training (balance and DTI difference scores) with the time since injury (# months between the head injury and the pre-test session). None of the correlations was significant using a conservative Bonferroni corrected threshold. Nevertheless, one moderate correlation was observed between the change in FA (post- minus pre-test) in the whole cerebellum and the time since injury, which was significant using an uncorrected significance threshold ( $r = -0.56$ , uncorrected  $p < 0.05$ ). This may suggest that the training has a higher effect on the cerebellar microstructure in patients who were in an earlier stage of recovery, possibly suggesting that these patients benefit more from training.

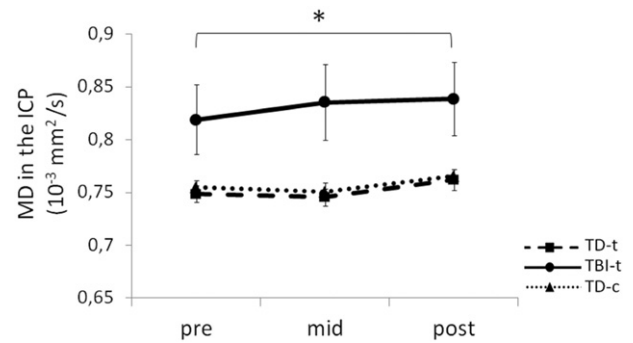


Fig. 5. Results of the MD in the ICP over the time course of the training (error bars indicate SEM, asterisk indicates significant difference).

## 4. Discussion

This study demonstrated WM microstructural alterations as well as balance control deficits in TBI patients as compared to controls. However, intensive balance training resulted in postural control improvements (as measured by force plate recordings) and associated alterations in the cerebellar WM microstructure in young TBI patients, particularly in the inferior cerebellar peduncle (ICP). To the best of our knowledge, this is the first time that relationships between cerebellar WM structure and training-induced postural control changes are established in a clinical group of young TBI patients and a typically developing group.

### 4.1. Postural control: group effects

Measurable postural control deficits in TBI patients are not always prominent in standard clinical/neurological examinations (Geurts et al., 1996; Kaufman et al., 2006; Basford et al., 2003; Gagnon et al., 2004) or in normal standing conditions (Kaufman et al., 2006; Basford et al., 2003). Here, we increased postural task difficulty by using more dynamic conditions (RWS and LOS subtests of the EquiTest System) or by manipulation of sensory input availability/reliability (using the SOT test protocol). Our results showed disturbed balance control in TBI subjects both on a static test with compromised sensory feedback (SOT) and on the more dynamic tests (RWS, LOS). This is consistent with

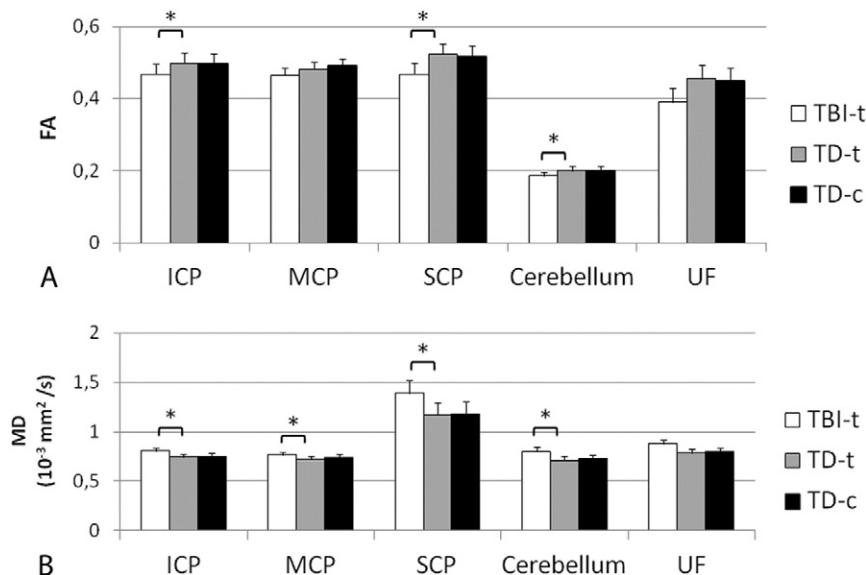


Fig. 4. Average FA and MD in the pre-test in the 5 ROIs for each group (error bars indicate SD). Comparisons of interest were made between TBI-t and TD-t as well as between TD-t and TD-c. Asterisks indicate significant differences.

**Table 2**

Results of cross-sectional correlation analysis between diffusion metrics and balance scores.

Group	ROI	FA				MD			
		Cerebellum	ICP	MCP	SCP	Cerebellum	ICP	MCP	SCP
TBI-t	SOT balance score	0.20 p = 0.437	0.42 p = 0.081	0.16 p = 0.524	<b>0.49*</b> <b>p = 0.0378</b>	−0.22 p = 0.400	<b>−0.56*</b> <b>p = 0.017</b>	−0.42 p = 0.081	−0.46 p = 0.053
	LOS directional control	0.36 p = 0.156	<b>0.50*</b> <b>p = 0.036</b>	0.37 p = 0.131	0.35 p = 0.159	0.01 p = 0.971	−0.28 p = 0.263	<b>−0.59*</b> <b>p = 0.011</b>	−0.23 p = 0.351
	RWS directional control	<b>0.67**</b> <b>p = 0.002</b>	0.18 p = 0.472	0.56* p = 0.014	<b>0.65**</b> <b>p = 0.002</b>	−0.42 p = 0.084	−0.45 p = 0.056	<b>−0.65**</b> <b>p = 0.002</b>	<b>−0.70**</b> <b>p = 0.0008</b>
TD-t	SOT balance score	0.18 p = 0.469	−0.06 p = 0.821	0.04 p = 0.876	0.08 p = 0.761	−0.32 p = 0.194	−0.04 p = 0.870	−0.44 p = 0.068	−0.07 p = 0.771
	LOS directional control	0.17 p = 0.502	0.01 p = 0.981	−0.07 p = 0.780	0.09 p = 0.724	0.06 p = 0.809	0.01 p = 0.976	−0.11 p = 0.653	−0.19 p = 0.445
	RWS directional control	<b>0.50*</b> <b>p = 0.035</b>	−0.03 p = 0.916	0.08 p = 0.750	0.25 p = 0.315	−0.06 p = 0.810	−0.18 p = 0.465	<b>−0.52*</b> <b>p = 0.027</b>	−0.46 p = 0.055
TD-c	SOT balance score	0.40 p = 0.247	0.32 p = 0.366	0.32 p = 0.365	0.37 p = 0.293	0.43 p = 0.220	−0.25 p = 0.494	0.057 p = 0.876	−0.18 p = 0.623
	LOS directional control	0.53 p = 0.112	0.51 p = 0.135	0.58 p = 0.082	0.09 p = 0.799	0.27 p = 0.464	−0.49 p = 0.152	−0.14 p = 0.692	0.19 p = 0.596
	RWS directional control	0.48 p = 0.163	0.33 p = 0.348	0.54 p = 0.110	0.24 p = 0.495	0.46 p = 0.177	−0.28 p = 0.426	−0.03 p = 0.938	−0.13 p = 0.710

\* Indicates correlations which were significant at  $p < 0.05$ , but did not survive corrections for multiple comparisons (i.e. multiple ROIs).

\*\* Indicates correlations which were significant using a Bonferroni corrected significance threshold.

previous studies reporting balance deficits in young and adult mild and more severe TBI patients by means of clinical tests (Geurts et al., 1996; Gagnon et al., 2004; Gagnon et al., 1998; Gagnon et al., 2001; Geurts et al., 1999), or the SOT (Caeyenberghs et al., 2010; Kaufman et al., 2006; Guskiewicz et al., 1997; Riemann, and Guskiewicz, 2000). However, in contrast to most previous studies using the SOT, a more direct measure of postural sway was used, based on the length of the center of pressure trajectory (i.e. the amount of body sway during the entire trial rather than the traditional SOT Equilibrium score which reflects the largest single body sway within a trial).

#### 4.2. Postural control: training effects

Significant practice-induced improvements in balance control were observed in both training groups. Long-term balance training effects have been demonstrated previously in older adults (Agmon et al., 2011) and in clinical populations, such as children with Down syndrome (Berg et al., 2012) and stroke patients (Gil-Gómez et al., 2011). Only one study so far documented training-induced improvements in a small sample of children (7–13 years) with chronic severe TBI ( $N = 5$ ), and cerebral palsy ( $N = 5$ ), using a home-based task-oriented program consisting of repetitive sit-to-stand and step-up exercises (Katz-Leurer et al., 2009). Here, we made use of PC-based training equipment, enabling storage of training information at the trial-by-trial level and monitoring of the compliance associated with home-based training. The gaming approach with-real time visual feedback resulted in a high compliance in both training groups. Such interactive training protocols are likely to play an important role in future rehabilitation settings. Similar devices, such as the commercially available wii Fit, have been used previously in clinical training studies with small patient samples or case studies (Agmon et al., 2011; Berg et al., 2012; Gil-Gómez et al., 2011; Goble et al., 2014; Esculier et al., 2012). However, these systems do mostly contain a stable/fixed platform, only allowing adaptations in difficulty level through changes in exercise games. In contrast, the pro-balance system comprises a dynamic/tilting platform. Adaptations in task difficulty throughout the training were enabled by adaptations in stability of the platform.

Specifically, we found that performance improvements in the TBI training group were significant on the two dynamic posturography test protocols (RWS and LOS tests) and on the SOT test with compromised sensory feedback. This positive transfer to various tests, which differed from the tasks used during training, reflects an increased

postural skill across various generic conditions that are relevant for daily life.

Improvements over time were also found in the TD-t group on each of the balance test protocols, suggesting that there is room for further balance improvement, even in healthy children and adolescents. These effects were not related to increasing familiarization with the test protocol since we did not observe training effects in the TD group without training. The addition of the latter group was a strong asset of the present study.

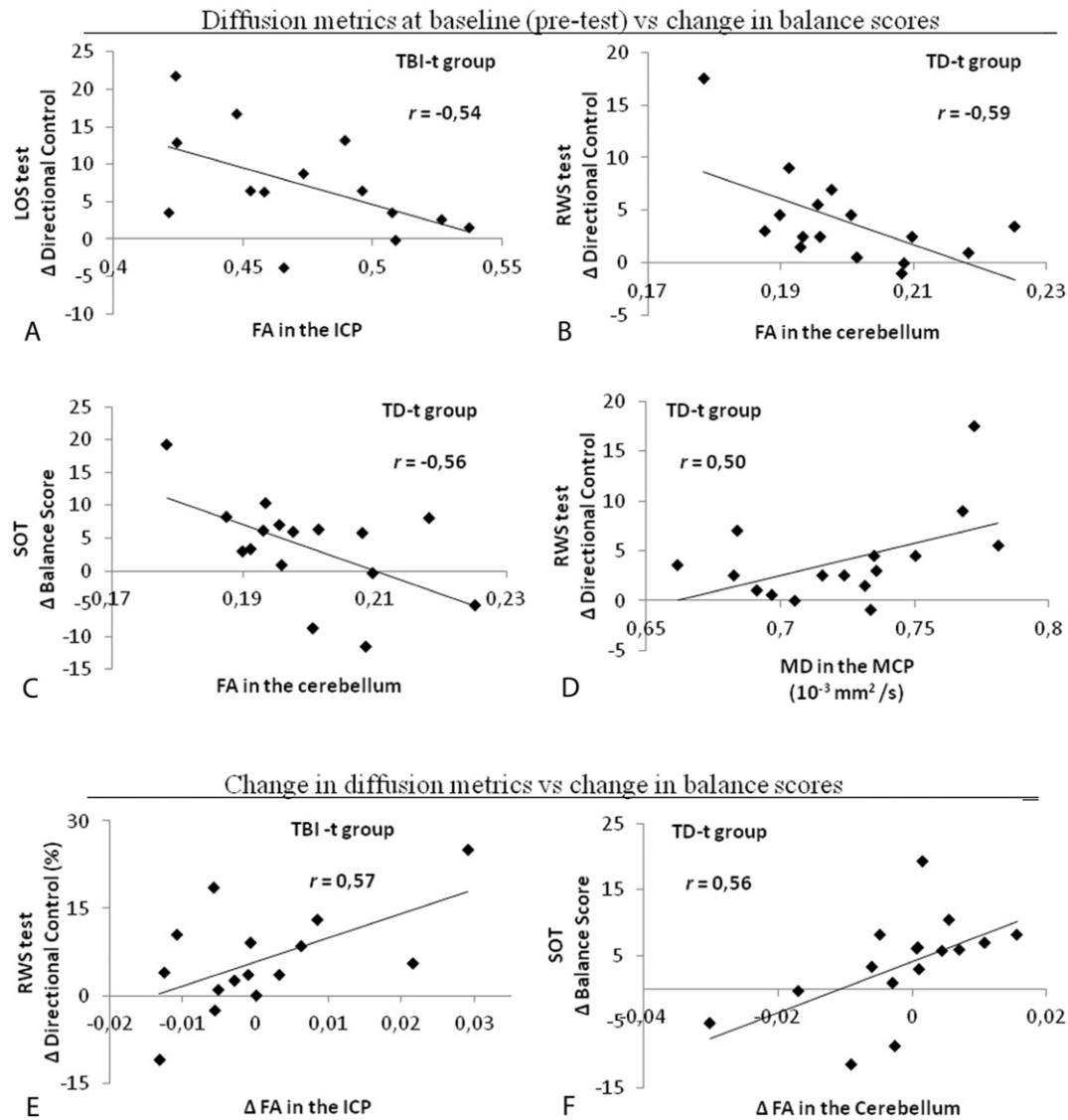
More research is required to investigate the temporal characteristics of these training effects. This would require an approach with more frequent measurement sessions throughout the training or a training device with an assessment of performance along with training difficulty during the entire training period.

#### 4.3. Diffusion MRI: group and training effects

Compared to controls, TBI patients showed significantly lower FA and higher MD in the cerebellum/cerebellar peduncles. This is consistent with previous work in TBI patients for tracts associated with sensorimotor functioning or cognitive control (Caeyenberghs et al., 2010; Huisman et al., 2004; Kraus et al., 2007; Sidaros et al., 2008; Wilde et al., 2012). Our previous study showed decreased FA values in pediatric TBI patients in the cerebellum, posterior thalamic radiation and corticospinal tract. Moreover, FA in several sensorimotor tracts was significantly correlated with balance deficits in TBI patients (Caeyenberghs et al., 2010). Here, we specifically demonstrated TBI-related WM differences in the SCP, ICP and cerebellum. This is consistent with previous research in pediatric populations between 8 and 18 years of age, showing that the cerebellum is highly vulnerable to WM damage following traumatic insult (Caeyenberghs et al., 2010; Spanos et al., 2007). Consistent with Caeyenberghs et al. (2010) (Caeyenberghs et al., 2010), performance on balance tests was convincingly associated with diffusion metrics of the cerebellum and cerebellar peduncles.

Interestingly, WM microstructure of the ICPs in young chronic TBI patients was altered as a result of intensive balance training. A significant increase from the pre- to post-test in MD of the ICP in the TBI-training group was found. Additionally, analysis of AD and RD in this tract revealed a significant increase in AD from pre- to post-test in the same group. Information carried through the ICP plays a crucial role in balance control. Vestibulocerebellar tracts in the ICP consist of both cerebellar efferent and afferent fibers to and from the vestibular nuclei. The ICP also contains fibers from the spinocerebellar tract, carrying sensory





**Fig. 6.** Scatter plots indicating the relationship between: A–D) baseline diffusion parameters (at pre-test) and difference scores on the balance tests (post-test minus pre-test); E) difference scores in FA in the ICP and directional control on the RWS (post-test minus pre-test) in the TBI-T group and F) difference scores in FA in the cerebellum and balance scores on the SOT (post-test minus pre-test) in the TD-T group.

information about the body parts (proprioception) to the spinocerebellum (Thach and Bastian, 2004). In healthy adults an increase in MD has been reported in the right cerebellar hemisphere after 6 weeks of balance training (Taubert et al., 2010). Moreover, balance training in patients with cerebellar degeneration has demonstrated an increase in cerebellar GM volume (Burciu et al., 2013).

Important to note, the direction of the change in the ICP (increase in MD and AD) was against our expectations. More specifically, previous training studies using different tasks have often demonstrated increases in FA and/or decreases in MD (Keller, and Just, 2009; Scholz et al., 2009; Takeuchi et al., 2010). However, our findings are in line with a previous longitudinal diffusion MRI study using a balance training protocol in healthy adults (Taubert et al., 2010), also demonstrating an increase in MD (right cerebellar and right inferior parietal WM regions) along with a decrease in FA (bilateral prefrontal WM regions) in response to training. Furthermore, studies on musicians and professional ballet dancers, have shown an increased MD (musicians) and decreased FA (ballet dancers) associated with increased sensorimotor training (Imfeld et al., 2009; Hänggi et al., 2010). Possible explanations for these discrepancies in the direction of diffusion changes are the different training protocols (training time and intensities) and/or differences

in the proportion of task-engaged fibers to other fibers within a voxel of interest as well as in the underlying fiber anatomy (Taubert et al., 2010). In the presence of crossing fibers, structural enhancement may have opposite effects on FA and MD when the altered fibers are not part of the dominant fiber direction (Jbabdi et al., 2010). Moreover, FA and MD can be modulated by many different properties of axonal fibers (Beaulieu, 2002). As such, diffusion MRI parameters can be regarded as potentially *sensitive* markers of microstructural plasticity but fail so far to provide *specific* information about the exact underlying cellular/biological processes. Yet, our finding of an increased AD may provide some indications about possible mechanisms of change. One possible mechanism underlying increase in AD is changes in fiber anatomy to a straighter and more parallel orientation which can increase diffusion along the axon (Takahashi et al., 2000). On the other hand, an elevated AD has also been associated with decreased WM integrity (Caeyenberghs et al., 2010; Kumar et al., 2013; Della Nave et al., 2011).

An additional complexity is that, in brain injury, WM tracts can already be affected by numerous cellular/molecular processes that influence diffusion of water molecules, such as demyelination, axonal loss and Wallerian degeneration (Beaulieu, 2002). It is fair to state that, with the current state of research on structural plasticity, it is too early

to make bald statements about the direction of training-induced change in diffusion metrics. More research is critically needed. Future studies should therefore include more tissue specific diffusion indices to assess structural plasticity, such as the composite hindered and restricted model of diffusion (CHARMED) (Assaf et al., 2004), apparent Fibre Density (Raffelt et al., 2012) or orientationally invariant indices of axon diameter and density (Alexander et al., 2010).

Even though some caution is warranted for interpretation of the present diffusion findings, our study has some strengths according to the criteria recently proposed by Thomas and Baker (Thomas and Baker, 2013). First, we made use of predefined ROIs based on anatomical hypotheses. As opposed to previous balance training studies using whole brain analyses, we used a small selection of predefined ROIs which reduces the chance of artificial findings. Second, our specific method of ROI definition was observer independent, avoiding normalization and associated bias towards one of the time points. Third, to obtain anatomic specificity of our findings, a control tract, mainly involved in cognitive processing (i.e. uncinate fasciculus), was selected, showing no significant changes with training. Finally, to test for specificity of training effects, we included a control group who underwent all the test sessions, yet without attending the training intervention (TD-c group). Such control groups have often been lacking in previous diffusion MRI or Voxel-based Morphometry studies using balance training protocols for understandable reasons (Taubert et al., 2010; Sehm et al., 2014; Burciu et al., 2013).

#### 4.4. Associations between baseline diffusion metrics and training-induced balance improvement

Correlation analysis was used to assess the ability of baseline diffusion variables to predict improvements in balance control. Correlation analysis considers each individual increase or decrease in balance parameters separately and was therefore tested regardless of whether or not an average group change was significant in mixed model analysis. Using an explorative significance threshold, we demonstrated that in both training groups, lower FA and/or a higher MD in the cerebellum or cerebellar peduncles (obtained at pretest) were associated with larger increases in balance performance over time (Fig. 6A–D).

The present results suggest that the status of WM structure in the cerebellar peduncles does not only predict balance performance directly (Caeyenberghs et al., 2010) but also reveals the potential for exercise-induced improvements in balance control. Even though it remains unclear which underlying microstructural properties can account for this association, higher MD or lower FA metrics in the cerebellum/peduncles may leave more room for structural adaptations that support improvements in balance control. Relationships between baseline brain metrics and training outcome have been investigated previously in brain injured children (aged 7–17 years), showing that FA at lesion sites was predictive of clinical improvement (gross motor function and upper limb function) following movement therapy (Rocca et al., 2013). Moreover, in the same study, baseline functional connectivity of the cerebellum was found to be predictive of improvements on gross motor performance at 6 months after therapy. This opens perspectives for the use of MRI-based metrics as valuable prognostic markers in the rehabilitation of TBI patients.

#### 4.5. Associations between changes in brain structure and training-induced changes in postural control

Balance improvements over the training period were correlated with degree of WM microstructural alterations. This resulted in a positive correlation in the TBI-training group between change in performance on the RWS and change in ICP FA, indicating that higher improvements were observed in subjects with more increase in FA during the training period (Fig. 6E). A similar positive relationship was found in the control-training group between increase in cerebellar FA

and degree of improvement in balance performance on the SOT (Fig. 6F). This suggests that a training-induced increase in FA in the ICP or cerebellum can support training-induced improvement of balance control. As expected, no correlations were found in our control ROI, the UF.

Few studies have correlated behavior with training related structural changes (but see Engvig et al., 2012 for memory training and Keller, and Just, 2009 for remediation training). Regarding balance training specifically, Sehm et al. (Sehm et al., 2014) demonstrated a correlation between GM changes in the precuneus and in several regions of the cerebral cortex with performance improvements on a balancing task. Finally, Taubert et al. (Taubert et al., 2010) demonstrated a negative correlation between cortical GM volume of the left cerebellum and improvements on a whole-body dynamic balancing task in healthy adults.

Our findings further support the important role of the cerebellum in (the recovery of) balance control (Morton, and Bastian, 2004; Manzoni, 2005; Konczak et al., 2005; Dichgans, and Mauritz, 1983). However, until now there has only been cross-sectional evidence for a direct association between the WM of the cerebellum/peduncles and motor/balance performance. Our previous study (Caeyenberghs et al., 2010) was the first to report strong correlations between diffusion MRI measures in the cerebellum/cerebellar peduncles and balance performance in a pediatric TBI population (aged 8–20 years). Previous studies on older adults with impaired mobility or on patients with inherited cerebellar disorders (spinocerebellar or Friedreich's ataxia) have reported decreased FA in ICP and/or SCP (Mandelli et al., 2007; Della Nave et al., 2008; Alcauter et al., 2011; Cavallari et al., 2013). These studies hereby demonstrated that diffusion MRI metrics of the cerebellar peduncles have considerable clinical impact on motor performance. Our present study adds to this work, suggesting associations between balance improvement over time and microstructural changes in cerebellar WM.

#### 4.6. Methodological considerations and conclusions

In the present study we have shown that generic training-induced improvements in balance control are associated with cerebellar WM microstructural alterations in young healthy and brain-injured subjects. However, a few limitations should be addressed. One issue requiring consideration is that our study did not account for possible volumetric changes in the cerebellum. Cerebellar volume has been shown to be decreased in TBI patients (Spanos et al., 2007). Further work should be done to elucidate the associations between alterations in WM microstructure and volume changes in TBI patients.

Another, possible limitation is that a priori pairwise comparisons were made to be able to explore the effects of training within each group. From a clinical point of view, analyzing changes in separate groups can be more informative than the finding of a main effect of time across both groups (i.e. main training effect). Results of the within-group pairwise comparisons should however be interpreted with caution, as we did not find any interaction effects between time and group indicating that, although there was an effect of training, it was not significantly different between the groups.

Finally, changes in diffusion parameters were small and were not significant in many ROIs. This is however not fully against our expectations. Realistically, changes in microstructural organization in WM (i.e. within subject effects) within a limited duration (weeks or even months) can be expected to be subtle and difficult to detect (Thomas and Baker, 2013; Holtmaat and Svoboda, 2009) as opposed to between subject effects. This may explain why significant alterations were detected in only one ROI. We further want to emphasize that studies concerning training-induced changes in white matter are scarce and relatively recent. It is still a developing domain (Thomas and Baker, 2013; May, 2011). In fact, the current study is the first comprehensive intervention study on balance control with young TBI patients in which behavioral and structural brain metrics are combined. Our findings

emphasize the critical role of the cerebellum and associated peduncles for postural control and they provide important hints towards training-induced structural plasticity that may drive behavioral improvement in young TBI patients.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.nicl.2014.12.006>.

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